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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,313	01/14/2005	Joon Youb Lee	2298.0080002	9295

26111 7590 04/22/2008

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EXAMINER	
HILL, KEVIN KAI	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
04/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,313	LEE ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-60* is/are pending in the application.

4a) Of the above claim(s) *31 and 40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,30,32-39 and 41-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 20, 2008 has been entered.

The Examiner has considered Applicant's Exhibits in the papers filed February 20, 2008.

Amendments

In the reply filed February 20, 2008, Applicant has cancelled claims 1-28, withdrawn claim 31, and entered new claims 29-60.

Applicant has elected the Her-2/neu plasmid construct species "a", a Her2/neu plasmid construct, wherein the human Her-2/neu gene has the nucleotide sequence of SEQ ID NO:2, and the cytokine species "GM-CSF".

Election of Applicant's invention(s) was made without traverse. Because Applicant did not distinctly and specifically point out the supposed errors in the Group or species restriction requirement, the election has been treated as an election without traverse and the restriction and election requirement is deemed proper and therefore made final (MPEP § 818).

Claims 31 and 40 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 29-30, 32-39 and 41-60 are under consideration.

Priority

This application is a 371 of PCT/KR03/01400, filed July 15, 2003, and claims priority to KR 10-2002-0041764, filed July 15, 2002 and KR 10-2003-0038012, filed June 12, 2003.

Acknowledgment is made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d).

In the response filed July 17, 2007, Applicant has submitted a certified translation of Korean Patent Application No. 10-2002-0041764, filed July 16, 2002 and Korean Patent Application No. 10-2003-0038012, filed June 12, 2003.

Accordingly, the effective priority date of the instant application is granted as July 16, 2002.

Examiner's Note

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the February 20, 2008 response will be addressed to the extent that they apply to current rejection(s).

Claim Objections

1. **Claim 29 is objected to because of the following informalities:** the comma (line 3) after Her-2/neu should be removed because its presence indicates that the alternative embodiment "comprising a nucleotide sequence encoding... the entire extracellular domain" is not necessarily a C-terminally truncated human Her-2/neu protein and may further comprise other polypeptide sequences, e.g. full-length Her-2/neu. The removal of the comma would place both alternatives under the phrase "a C-terminally truncated human Her-2/neu protein consisting essentially of" which is considered consonant with the instant specification.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

2. **Claims 47-60 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claims 47, 49, 52, 55 and 59 (and dependent claims) are vague and indefinite in that no step(s) in the claimed method refers back to or recapitulates the preamble of the claim. Applicants recite a method of preventing or treating cancer, inducing antitumor

immunity, reducing tumor growth, decreasing tumor metastasis and prolonging survival, but no step is recited that actually accomplishes the preamble. It is unclear if additional, undisclosed steps are a part of the claimed method and therefore the metes and bounds of the claimed subject matter are unclear.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. **The prior rejection of Claims 16 and 19-28 under 35 U.S.C. 112, first paragraph, is withdrawn** in light of Applicant's cancellation of the claims.

4. **Claims 49-60 are rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is applied to the newly added claims, yet is essentially the same argument set forth in the prior Office Actions and is maintained for reasons of record, re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed February 20, 2008.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

With respect to the method, the claim is broad for encompassing treatment methods as applied to humans, wherein Applicant contemplates an enormous genus of DNA vaccine formulations and administration means, for example, aerosol formulation/administration, parenteral injection, suppositories, and oral formulations (pgs 9-10).

With respect to the DNA vaccine composition, the breadth of the claim is exceptionally large for encompassing a genus of structurally distinct nucleic acid compositions encoding structurally and biologically distinct polypeptides for use as a DNA vaccine for the treatment and/or prevention of Her-2/neu-over-expressing cancers, including carcinoma of the breast, prostate, ovary, uterus, stomach and adenocarcinoma of the lung.

When the claims are analyzed in light of the specification, the inventive concept of the instant application is to provide a DNA vaccine composition for preventing or treating cancer, wherein the specification discloses that Her-2/neu is amplified and over-expressed in several types of human adenocarcinomas, especially tumors of the breast and ovary. Thus, the Her-2/neu oncogene is an excellent target for the development of therapeutic vaccines specific for Her-2/neu-over-expressing human cancers (pg 1, lines 15-28).

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

Her-2/*neu* is an oncogene coding for a transmembrane protein (p185neu) and belonging to the family of tyrosine kinase growth factor receptors. Her-2/*neu* gene amplification and consequent over expression of Her-2/*neu* receptor have been observed in a significant proportion of human cancers including carcinoma of the breast, prostate, ovary, uterus, stomach and adenocarcinoma of the lung and is intimately associated with malignant phenotype and aggressiveness of the malignancy. The relevant art of the instant invention is DNA vaccines, wherein the level of skill for an ordinary artisan is high.

DNA Vaccine

At the time of the instant application (priority date of July, 2002), limited data was available regarding DNA vaccination in humans. In the early trials, eliciting anti-tumor immunity in cancer patients using DNA vaccines has proved more difficult, and little evidence of anti-tumor immunity was demonstrated using first generation tumor antigen DNA vaccines.

DNA vaccine model represents a promising, practical and effective way to elicit immune responses against an antigen expressed by malignant cells. An issue in developing tumor DNA vaccines is to design protocols that can be translated from murine models to large animal models and clinical human use without losing their potency (Smorlesi et al, Vaccine 24: 1766-1775, 2006, pg 1767, col. 1, ¶1). The quality of the immune response elicited by a DNA vaccine is also dependent by the procedure of DNA delivery that influences the mechanisms of DNA uptake, transgene expression, and transgene product processing. The results of tumor antigen DNA vaccine approaches might be improved by optimization of key variables such as dosage, route,

vector design, and boosting strategies. Thus, the role of the DNA delivery system on the outcome of the vaccine should be considered in the elaboration of a HER2/*neu* DNA vaccine.

The efficacy of DNA vaccine against HER2/*neu* is influenced by the method of release of DNA. Smorlesi et al showed that vaccine delivery methods, e.g. intramuscular injection, electroporation, and gene gun, elicited diverse immune mechanisms that differently prevented the appearance and the development of spontaneous mammary carcinomas (Smorlesi et al; pg 1773, col. 1, ¶1). The art also recognizes that the non-obvious use of a particular promoter for required expression in the desired cell type. For example, SV40, although a relatively strong promoter in fibroblasts and epithelial cell types, may be weaker than the commonly used cytomegalovirus promoter. (Chen et al, Clinical Cancer Research 6: 4381-4388, 2000; pg 4385, col. 2).

Many of the experimental systems used to evaluate the efficacy of DNA vaccine against tumor progression suffer several drawbacks, for example, immunization of healthy animals against a subsequent challenge with tumor cells was assayed rather than treatment of a tumor-bearing animal with DNA vaccine. However, patients with established, rapidly growing tumors can have an impaired cellular and humoral immune system. Therefore, it might be difficult to activate immunological defense mechanisms by vaccination (Bernhard et al, Society for Endocrinology 9(1): 33-44, 2002; pg 40, col. 1, ¶1). Moreover, while the amount of produced antibodies only partially correlate with the outcome of vaccination, the quality of humoral response seems to be determinant for the success of vaccination. Immunized mice can develop anti-Her-2/neu antibody, as demonstrated by Western blotting, but are provided no protection from tumor progression (Chen et al; pg 4385, col. 2, lines 15-17). Therefore, it is likely that DNA vaccine against a specific tumor-associated antigen may not be sufficient by itself to prevent progression of native pre-existing tumor.

The art also recognizes that a number of concerns exist with respect to immunizing with Her-2/neu vaccines. For example, once concern is that the polyclonal humoral response generated may contain immunoglobulins that can activate the Her-2/neu receptor, as has been found with some monoclonal antibodies, and lead to increased cell growth rather than inhibition (Esserman et al, Cancer Immunol. Immunther. 47: 337-342, 1999; pg 340, col. 2, ¶3). Furthermore, it is possible that increasing the anti-Her-2/neu immunity to a level necessary to destroy cancer tissue *in vivo* may also increase levels of autoimmune reactivity against normal tissues to the point of inducing toxicity (Esserman et al; pg 341, col. 1, lines 17-21).

Animal models

Most DNA vaccine investigations are performed in models of implanted tumors that consist of the challenge of mice with a bolus of tumor cells giving rise to a fast and unnaturally growing tumor. Furthermore, the roles of p185Her-2/neu on tumor growth and immunomodulation may be altered in tumors over-expressing rat or human p185Her-2/neu. The therapeutic response may thus depend on the type of vaccine administered as well as the cancer cells used in the animal study (Lin et al, Molecular Therapy 10(2): 290-301, 2004; pg 296, col. 1, lines 11-14). Therefore, the efficacy of Her-2/neu DNA vaccine must be tested on mouse tumor cells natively over-expressing mouse p185Her-2/neu (Lin et al, pg 291, col. 1, ¶1). The art recognizes that transgenic mice reproduce the more complex spontaneous progression of a pre-neoplastic lesion and their use provides information that may be more relevant to cancer

development in humans where the tumor is initiated by the clonal expansion from a single cell *in vivo* (Smorlesi et al; pg 1767, col.s 1-2, joining ¶). For example, the *Her-2/neu* transgenic mice possess distinct kinetics of disease development that better reflect spontaneous mammary carcinogenesis and recapitulate a few features of the development of human mammary carcinoma.

Although the results using plasmid DNA vaccines against HER2 have been promising in rodent models, there are drawbacks when considering the use of plasmid DNA vaccines in humans. The major drawback to the use of plasmid DNA vaccines in humans is that, although proven to be quite effective in rodents, DNA-based vaccines have generally performed poorly in both non-human primate studies as well as in human clinical trials. Thus, until formulation and delivery technologies are developed to increase the potency of plasmid DNA vaccines in humans, this approach is not likely to be an optimal one for human vaccines (Foy et al, Seminars in Oncology 29(3 Suppl. 11): 53-61, 2002; pg 56, col. 2, ¶1). Furthermore, the art recognizes that FVB and BALB/c mice used for testing experimental DNA vaccines may not be representative for the human scenario (Chang et al, Int. J. Cancer 111: 86-95, 2004; pg 86, col. 1, last sentence). In the case of human Her-2/neu in human patients, the artisan may not reasonably extrapolate the ability to breakdown tolerance and induce an effective immune response, as achieved in animal models, because Her-2/neu is a self-tolerated antigen widely expressed at low levels in multiple tissues in humans.

Cytokine therapy

Cytokine genes have been used in many studies to enhance the immune response to a DNA vaccine against a specific antigen. Fusion genes or co-delivery of cytokine genes can augment the immune response and influence the immune pathway. The anti-tumor responses induced by different cytokines seemed to operate through different mechanisms. For example, cytotoxic CD8+ T cells play a major role in the IL-2-induced immune response, whereas CD4+ and CD8+ T cells mediate the GM-CSF anti-tumor activity (Chen et al; pg 4381, col. 2, ¶1). Although several studies have indicated that GM-CSF had a strong capacity to enhance the effects of DNA vaccines by amplifying both cellular and humoral immunity, the benefit of co-administration of cytokine genes is dependent on the nature of tumor-associated antigen and the intrinsic immunologic properties of tumor cells (Lin et al; pg 298, col. 1, ¶1).

Thus, the art recognizes significant unpredictability regarding the design of any Her-2/neu DNA vaccine, with or without combined administration of nucleic acids encoding a cytokine, to reliably prevent or treat an enormous genus of etiologically and pathologically distinct tumors in an enormous genus of mammalian organisms, including mice and humans. The art speaks to the lack of standards in animal models, the difficulties to adequately mimic the complex disease pathologies observed in humans to the animal model system, and the general inability to reliably extrapolate results achieved in the rodent system to the primate system.

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

The specification teaches the tumor challenge in laboratory BALB/c mice by injection of suspended human breast carcinoma cells or murine colon adenocarcinoma cells (pg 13, lines 1-5), wherein said cells either administered subcutaneously on the flank or intravenously (pg 15,

lines 29-30). Applicant contemplates an enormous genus of DNA vaccine formulations and administration means (pgs 9-10); however, only intramuscular injection is disclosed as an effective administration means of vaccination. The specification also does not teach the structural nature of the expression plasmids; merely disclosing that the pCK vector has a stronger promoter activity than pTV2 (pg 22, line 18). Furthermore, the claims reasonably embrace a pTV2Neu$_{TM}$-GMCSF bi-cistronic expression plasmid, yet no such plasmid is disclosed in the specification. The inventive DNA vaccines are administered either before or after the tumor challenge by intramuscular injection. Under experimentally controlled conditions, the vaccinated mice were able to generate antibodies to the Her-2/neu antigen (Example 3), suppress tumor challenge, exhibit decreased frequency of tumor metastasis, and prolonged survival periods (Examples 4-6).

The specification fails to disclose that the inventive method is capable of achieving the clinically desirable results as per spontaneous tumor formation, which is the clinically relevant condition, in any other mammal, including primates such as humans. Such guidance is important in light of the wealth of data in the art teaching the inability to predictably extrapolate the instant rodent model to humans.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

Thus, the quantity of necessary experimentation to make or use the invention as claimed, based upon what is known in the art and what has been disclosed in the specification, will create an undue burden for a person of ordinary skill in the art to demonstrate that the instantly claimed DNA vaccine compositions can prevent or treat an enormous genus of etiologically and pathologically distinct cancers, as contemplated by Applicant and reasonably embraced by the claims, via the enormous genus of contemplated composition formulations and administration means because the critical and essential elements of the DNA vaccine expression plasmids are not disclosed so as to guide an artisan how to make the DNA vaccine compositions and effectively target the nucleic acid to the desired cell types so as to effect the immunological response. Furthermore, the art recognizes that the model system disclosed, wherein a bolus of tumor cells is administered to the host, does not adequately represent the clinical condition wherein a patient has any one of an enormous genus of genotypically and phenotypically distinct cancers in any one of a multitude of physiologically and pathologically distinct organs and tissues.

In conclusion, the specification fails to provide any guidance as to how an artisan would have dealt with the art-recognized limitations of the claimed methods. Accordingly, the instant claims are rejected for failing to comply with the enablement requirement.

5. **Claims 47-48 are rejected under 35 U.S.C. 112, first paragraph**, because the specification, while being enabling for methods of preventing and treating a Her-2/neu-over-expressing cancer in a rodent, the method(s) comprising the step of administering by intramuscular injection an effective amount of a DNA vaccine composition comprising a pTV2

vector or pCK vector which comprises a nucleotide sequence encoding a truncated human Her-2/neu protein, said truncated human Her-2/neu protein lacking an intracellular domain, and wherein said DNA vaccine composition further comprises a nucleic acid encoding the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF), does not reasonably provide enablement for a method of preventing or treating an enormous genus of mammalian subjects, including humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

This rejection is applied to the newly added claims, yet is essentially the same argument set forth in the prior Office Actions and is maintained for reasons of record, re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed February 20, 2008.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

With respect to the method, the claim is broad for encompassing treatment methods as applied to an enormous genus of subjects, including mammals, specifically humans, wherein Applicant contemplates an enormous genus of DNA vaccine formulations and administration means, for example, aerosol formulation/administration, parenteral injection, suppositories, and oral formulations (pgs 9-10).

With respect to the DNA vaccine composition, the breadth of the claim is exceptionally large for encompassing a genus of structurally distinct nucleic acid compositions encoding structurally and biologically distinct polypeptides for use as a DNA vaccine for the treatment

and/or prevention of Her-2/neu-over-expressing cancers, including carcinoma of the breast, prostate, ovary, uterus, stomach and adenocarcinoma of the lung.

When the claims are analyzed in light of the specification, the inventive concept of the instant application is to provide a DNA vaccine composition for preventing or treating cancer, wherein the specification discloses that Her-2/neu is amplified and over-expressed in several types of human adenocarcinomas, especially tumors of the breast and ovary. Thus, the Her-2/neu oncogene is an excellent target for the development of therapeutic vaccines specific for Her-2/neu-over-expressing human cancers (pg 1, lines 15-28).

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

Her-2/*neu* is an oncogene coding for a transmembrane protein (p185neu) and belonging to the family of tyrosine kinase growth factor receptors. Her-2/*neu* gene amplification and consequent over expression of Her-2/*neu* receptor have been observed in a significant proportion of human cancers including carcinoma of the breast, prostate, ovary, uterus, stomach and adenocarcinoma of the lung and is intimately associated with malignant phenotype and aggressiveness of the malignancy. The relevant art of the instant invention is DNA vaccines, wherein the level of skill for an ordinary artisan is high.

DNA Vaccine

At the time of the instant application (priority date of July, 2002), limited data was available regarding DNA vaccination in humans. In the early trials, eliciting anti-tumor immunity in cancer patients using DNA vaccines has proved more difficult, and little evidence of anti-tumor immunity was demonstrated using first generation tumor antigen DNA vaccines.

DNA vaccine model represents a promising, practical and effective way to elicit immune responses against an antigen expressed by malignant cells. An issue in developing tumor DNA vaccines is to design protocols that can be translated from murine models to large animal models and clinical human use without losing their potency (Smorlesi et al, Vaccine 24: 1766-1775, 2006, pg 1767, col. 1, ¶1). The quality of the immune response elicited by a DNA vaccine is also dependent by the procedure of DNA delivery that influences the mechanisms of DNA uptake, transgene expression, and transgene product processing. The results of tumor antigen DNA vaccine approaches might be improved by optimization of key variables such as dosage, route, vector design, and boosting strategies. Thus, the role of the DNA delivery system on the outcome of the vaccine should be considered in the elaboration of a HER2/*neu* DNA vaccine.

The efficacy of DNA vaccine against HER2/*neu* is influenced by the method of release of DNA. Smorlesi et al showed that vaccine delivery methods, e.g. intramuscular injection, electroporation, and gene gun, elicited diverse immune mechanisms that differently prevented the appearance and the development of spontaneous mammary carcinomas (Smorlesi et al; pg 1773, col. 1, ¶1). The art also recognizes that the non-obvious use of a particular promoter for required expression in the desired cell type. For example, SV40, although a relatively strong promoter in fibroblasts and epithelial cell types, may be weaker than the commonly used cytomegalovirus promoter. (Chen et al, Clinical Cancer Research 6: 4381-4388, 2000; pg 4385, col. 2).

Many of the experimental systems used to evaluate the efficacy of DNA vaccine against tumor progression suffer several drawbacks, for example, immunization of healthy animals against a subsequent challenge with tumor cells was assayed rather than treatment of a tumor-bearing animal with DNA vaccine. However, patients with established, rapidly growing tumors can have an impaired cellular and humoral immune system. Therefore, it might be difficult to activate immunological defense mechanisms by vaccination (Bernhard et al, Society for Endocrinology 9(1): 33-44, 2002; pg 40, col. 1, ¶1). Moreover, while the amount of produced antibodies only partially correlate with the outcome of vaccination, the quality of humoral response seems to be determinant for the success of vaccination. Immunized mice can develop anti-Her-2/neu antibody, as demonstrated by Western blotting, but are provided no protection from tumor progression (Chen et al; pg 4385, col. 2, lines 15-17). Therefore, it is likely that DNA vaccine against a specific tumor-associated antigen may not be sufficient by itself to prevent progression of native pre-existing tumor.

The art also recognizes that a number of concerns exist with respect to immunizing with Her-2/neu vaccines. For example, once concern is that the polyclonal humoral response generated may contain immunoglobulins that can activate the Her-2/neu receptor, as has been found with some monoclonal antibodies, and lead to increased cell growth rather than inhibition (Esserman et al, Cancer Immunol. Immunther. 47: 337-342, 1999; pg 340, col. 2, ¶3). Furthermore, it is possible that increasing the anti-Her-2/neu immunity to a level necessary to destroy cancer tissue *in vivo* may also increase levels of autoimmune reactivity against normal tissues to the point of inducing toxicity (Esserman et al; pg 341, col. 1, lines 17-21).

Animal models

Most DNA vaccine investigations are performed in models of implanted tumors that consist of the challenge of mice with a bolus of tumor cells giving rise to a fast and unnaturally growing tumor. Furthermore, the roles of p185Her-2/neu on tumor growth and immunomodulation may be altered in tumors over-expressing rat or human p185Her-2/neu. The therapeutic response may thus depend on the type of vaccine administered as well as the cancer cells used in the animal study (Lin et al, Molecular Therapy 10(2): 290-301, 2004; pg 296, col. 1, lines 11-14). Therefore, the efficacy of Her-2/neu DNA vaccine must be tested on mouse tumor cells natively over-expressing mouse p185Her-2/neu (Lin et al, pg 291, col. 1, ¶1). The art recognizes that transgenic mice reproduce the more complex spontaneous progression of a pre-neoplastic lesion and their use provides information that may be more relevant to cancer development in humans where the tumor is initiated by the clonal expansion from a single cell *in vivo* (Smorlesi et al; pg 1767, col.s 1-2, joining ¶). For example, the *Her-2/neu* transgenic mice possess distinct kinetics of disease development that better reflect spontaneous mammary carcinogenesis and recapitulate a few features of the development of human mammary carcinoma.

Although the results using plasmid DNA vaccines against HER2 have been promising in rodent models, there are drawbacks when considering the use of plasmid DNA vaccines in humans. The major drawback to the use of plasmid DNA vaccines in humans is that, although proven to be quite effective in rodents, DNA-based vaccines have generally performed poorly in both non-human primate studies as well as in human clinical trials. Thus, until formulation and delivery technologies are developed to increase the potency of plasmid DNA vaccines in

humans, this approach is not likely to be an optimal one for human vaccines (Foy et al, Seminars in Oncology 29(3 Suppl. 11): 53-61, 2002; pg 56, col. 2, ¶1). Furthermore, the art recognizes that FVB and BALB/c mice used for testing experimental DNA vaccines may not be representative for the human scenario (Chang et al, Int. J. Cancer 111: 86-95, 2004; pg 86, col. 1, last sentence). In the case of human Her-2/neu in human patients, the artisan may not reasonably extrapolate the ability to breakdown tolerance and induce an effective immune response, as achieved in animal models, because Her-2/neu is a self-tolerated antigen widely expressed at low levels in multiple tissues in humans.

Cytokine therapy

Cytokine genes have been used in many studies to enhance the immune response to a DNA vaccine against a specific antigen. Fusion genes or co-delivery of cytokine genes can augment the immune response and influence the immune pathway. The anti-tumor responses induced by different cytokines seemed to operate through different mechanisms. For example, cytotoxic CD8+ T cells play a major role in the IL-2-induced immune response, whereas CD4+ and CD8+ T cells mediate the GM-CSF anti-tumor activity (Chen et al; pg 4381, col. 2, ¶1). Although several studies have indicated that GM-CSF had a strong capacity to enhance the effects of DNA vaccines by amplifying both cellular and humoral immunity, the benefit of co-administration of cytokine genes is dependent on the nature of tumor-associated antigen and the intrinsic immunologic properties of tumor cells (Lin et al; pg 298, col. 1, ¶1).

Thus, the art recognizes significant unpredictability regarding the design of any Her-2/neu DNA vaccine, with or without combined administration of nucleic acids encoding a cytokine, to reliably prevent or treat an enormous genus of etiologically and pathologically distinct tumors in an enormous genus of mammalian organisms, including mice and humans. The art speaks to the lack of standards in animal models, the difficulties to adequately mimic the complex disease pathologies observed in humans to the animal model system, and the general inability to reliably extrapolate results achieved in the rodent system to the primate system.

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

The specification teaches the tumor challenge in laboratory BALB/c mice by injection of suspended human breast carcinoma cells or murine colon adenocarcinoma cells (pg 13, lines 1-5), wherein said cells either administered subcutaneously on the flank or intravenously (pg 15, lines 29-30). Applicant contemplates an enormous genus of DNA vaccine formulations and administration means (pgs 9-10); however, only intramuscular injection is disclosed as an effective administration means of vaccination. The specification also does not teach the structural nature of the expression plasmids; merely disclosing that the pCK vector has a stronger promoter activity than pTV2 (pg 22, line 18). Furthermore, the claims reasonably embrace a pTV2Neu$_{TM}$-GMCSF bi-cistronic expression plasmid, yet no such plasmid is disclosed in the specification. The inventive DNA vaccines are administered either before or after the tumor challenge by intramuscular injection. Under experimentally controlled conditions, the vaccinated mice were able to generate antibodies to the Her-2/neu antigen (Example 3), suppress tumor challenge, exhibit decreased frequency of tumor metastasis, and prolonged survival periods (Examples 4-6).

The specification fails to disclose that the inventive method is capable of achieving the clinically desirable results as per spontaneous tumor formation, which is the clinically relevant condition, in any other mammal, including primates such as humans. Such guidance is important in light of the wealth of data in the art teaching the inability to predictably extrapolate the instant rodent model to humans.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

Thus, the quantity of necessary experimentation to make or use the invention as claimed, based upon what is known in the art and what has been disclosed in the specification, will create an undue burden for a person of ordinary skill in the art to demonstrate that the instantly claimed DNA vaccine compositions can prevent or treat an enormous genus of etiologically and pathologically distinct cancers, as contemplated by Applicant and reasonably embraced by the claims, via the enormous genus of contemplated composition formulations and administration means because the critical and essential elements of the DNA vaccine expression plasmids are not disclosed so as to guide an artisan how to make the DNA vaccine compositions and effectively target the nucleic acid to the desired cell types so as to effect the immunological response. Furthermore, the art recognizes that the model system disclosed, wherein a bolus of tumor cells is administered to the host, does not adequately represent the clinical condition wherein a patient has any one of an enormous genus of genotypically and phenotypically distinct cancers in any one of a multitude of physiologically and pathologically distinct organs and tissues.

In conclusion, the specification fails to provide any guidance as to how an artisan would have dealt with the art-recognized limitations of the claimed method commensurate with the scope of the claimed invention and therefore, limiting the claimed invention to methods of preventing and treating a Her-2/neu-over-expressing cancer in a rodent, the method(s) comprising the step of administering by intramuscular injection an effective amount of a DNA vaccine composition comprising a pTV2 vector or pCK vector which comprises a nucleotide sequence encoding a truncated human Her-2/neu protein, said truncated human Her-2/neu protein lacking an intracellular domain, and wherein said DNA vaccine composition further comprises a nucleic acid encoding the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF), is proper.

Applicant's Arguments

Applicant argues that:

a) mere breadth of a claim does not make a claim not enabled or indefinite as long as the scope of the subject matter that is embraced is clear. *In re Miller*, 441 F.2d 689 (CCPA 1971). See MPEP 2173.04.) Additionally, it is permissible for claims to encompass inoperative embodiments. See MPEP 2164.08(b);

b) an enabling disclosure allows for some experimentation even in large amounts as long as it is not undue. *In re Wands*, 858 F.2d 731,737 (Fed. Cir. 1988). In addition to working

examples, the specification includes guidance for administration, formulation and dosage of the plasmid constructs which a person of ordinary skill would find sufficient to make and use the claimed invention;

c) the present application has provided working examples in which Her-2/neu DNA vaccines were effective at providing antitumor immunity against human Her-2/neu expressing murine tumor cells (Her-2- CT26) in mice. Thus, none of the evidence or arguments set forth by the Examiner established that immune correlates of the present invention are "unbelievable" or "unpredictable." Patent law only requires a showing that "reasonable correlation" exists between the scope of the claims and the scope of enablement. As stated in the M.P.E.P. § 2164.02, "'correlation' as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use." If a particular model is recognized as correlating to a specific condition, then it should be accepted as such unless the Examiner has evidence that the model does not correlate. *In re Brana*, 51 F.3d 1560, (Fed. Cir. 1995), at 1566;

d) the PTO guidelines do not require proof of efficacy, and are, in fact, explicit on this point: "Office personnel should not impose on Applicants the unnecessary burden of providing evidence from human clinical trials. There is no decisional law that requires an Applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders." M.P.E.P. § 2107.03. The guidelines further state that "[t]he Office must confine its review of patent applications to the statutory requirements of the patent law, and in quoting *In re Brana*, supra, that "FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws"; and

e) a post-filing manuscript (attached herewith as Exhibit 3), co-authored by an inventor of the captioned application, reports that primate studies showed that "genetic vaccines efficiently elicited Her-2/neu-specific humoral and cellular immune responses without causing severe adverse effects in non-human primates[.]" See Exhibit 3, page 2. A pCK bicistronic truncated Her-2/neu and GM-CSF construct of the current invention was tested in primates.

Applicant's argument(s) has been fully considered, but is not persuasive.

With respect to a), the claims embrace a real-world use of the invention of significant economic and medical impact, namely treatment of humans suffering from Her-2/neu-over-expressing cancers. Thus, the inoperative embodiment, specifically prevention and treatment of humans, is a real-world consideration and fundamental flaw within the scope of the invention.

With respect to b), while the Examiner recognizes the mice, like humans, are susceptible to tumors, especially those surgically implanted by humans, the substantive issue is that the art recognizes many *in vitro* and animal models that are provided as evidence of success of treatment have not translated into successful treatment in humans. Applicant is respectfully reminded that the art recognizes a lack of standards in animal models, unpredictability regarding gene therapy and DNA vaccine technologies to elicit a specific immune response sufficient to achieve a clinically-relevant therapeutic outcome, and the limitations of animal models that, although proven to be quite effective in rodents, DNA-based vaccines have generally performed poorly in both non-human primate studies as well as in human clinical trials.

With respect to c), Applicant is respectfully referred to the subsection "Animal Models" above, copied herein, demonstrating that the post-filing art recognizes the inadequacies of animal models and their significant limitations to predictably correlate to human disease. Although the results using plasmid DNA vaccines against HER2 have been promising in rodent models, there are drawbacks when considering the use of plasmid DNA vaccines in humans. The major drawback to the use of plasmid DNA vaccines in humans is that, although proven to be quite effective in rodents, **DNA-based vaccines have generally performed poorly in both non-human primate studies as well as in human clinical trials. Thus, until formulation and delivery technologies are developed to increase the potency of plasmid DNA vaccines in humans, this approach is not likely to be an optimal one for human vaccines** (Foy et al, Seminars in Oncology 29(3 Suppl. 11): 53-61, 2002; pg 56, col. 2, ¶1). Furthermore, the art recognizes that FVB and BALB/c mice used for testing experimental DNA vaccines may not be representative for the human scenario (Chang et al, Int. J. Cancer 111: 86-95, 2004; pg 86, col. 1, last sentence). In the case of human Her-2/neu in human patients, the artisan may not reasonably extrapolate the ability to breakdown tolerance and induce an effective immune response, as

achieved in animal models, because Her-2/neu is a self-tolerated antigen widely expressed at low levels in multiple tissues in humans.

With respect to d), the Examiner has not required Applicant to provide evidence from human clinical trials to **establish utility** of the claimed invention. The claims are not rejected on the grounds of lack of utility. The substantive issue is that the instant specification does not enable the artisan **how to use** the inventive DNA vaccine plasmids in the claimed methods of treating an enormous genus of mammals, including humans. The prior and post-filing art teaches unpredictability for DNA vaccines in humans, and thus the artisan would need specific guidance from the instant specification to overcome the art-recognized obstacles and use the claimed invention in humans. Unfortunately for Applicant, the necessary specific guidance is absent.

With respect to e), the state of the art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. The specification must be enabling as of the filing date, not evidence provided several years after the date of filing. The state of the art for a given technology is not static in time. It is entirely possible that a disclosure filed on January 2, 1990, would not have been enabled. However, if the same disclosure had been filed on January 2, 1996, it might have enabled the claims. Therefore, the state of the prior art must be evaluated for each application based on its filing date (see MPEP 2164.05(a)). In the instant case, Exhibit 3 (Ko et al, 2005) provided by Applicants does not establish enablement of the claimed invention at the time of filing.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. The prior rejection of **Claims 1-3, 13, 16 and 19-28 are rejected under 35 U.S.C. 103(a)** as being obvious over Piechocki et al (J. Immunol. 167: 3367-3374, 2001) and Lee et al (Biochem. Biophys. Res. Comm. 272(1): 230-235, 2000), as evidenced by Bocchia et al (Haematologica 85: 1172-1206, 2000) **is withdrawn** in light of the cancellation of said claims.

7. **Claims 29-30, 32-39 and 41-60 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Piechocki et al (J. Immunol. 167: 3367-3374, 2001) in view of Erickson et al (WO 01/00244), Lee et al (J. Virol. 72(10):8430-8436, 1998), Lee et al (Biochem. Biophys. Res. Comm. 272(1): 230-235, 2000) and Chen et al (Cancer Res. 58:1965-1971, 1998; *of record in IDS), as evidenced by Bocchia et al (Haematologica 85: 1172-1206, 2000).

Determining the scope and contents of the prior art.

With respect to the claimed plasmid expression constructs, Piechocki et al teach a plasmid DNA vaccine comprising a nucleotide sequence encoding a truncated human Her-2/neu polypeptide, said polypeptide consisting of an extracellular domain, specifically the amino terminal amino acids 1-505 of the mature human Her-2/neu extracellular domain (pg 3368, col. 1, Construction).

Piechocki et al do not teach the truncated human Her-2/neu polypeptide to be encoded by a nucleic acid sequence comprising SEQ ID NO:2. However, Erickson et al is but one example demonstrating that the sequence of human Her-2/neu having 100% identity to SEQ ID NO:2 was known in the art prior to the instant invention (see attached Search Result for SEQ ID NO:2).

Piechocki et al do not teach the use of a pTV2 vector. However, at the time of the invention, Lee et al (1998) taught the eukaryotic expression vector pTV2 used to express a single

gene of interest, specifically GM-CSF, E1t or E2t, or as bi-cistronic expression plasmid to express a gene of interest in combination with GM-CSF, wherein the gene of interest and GM-CSF are separated by an internal ribosome entry site (IRES) (pg 8430, col. 2, Construction; pg 8431, Figure 1). Lee et al teach a pharmaceutical composition comprising either the bi-cistronic pTV2 vector comprising GM-CSF or a first pTV2 plasmid encoding a gene of interest in combination with a second pTV2 plasmid encoding GM-CSF, and a carrier, specifically sterile saline administered to rats in an experiment to ascertain if said vector is capable of immunization (pg 8432, col. 2; Table 1).

Neither Piechocki et al nor Lee et al (1998) teach a pCK vector. However, at the time of the invention, Lee et al (2000) taught the construction of a pCK expression plasmid that is able to drive high levels of gene expression *in vivo* for therapeutic use. Lee et al teach the use of this vector to express VEGF165 in mice when administered in combination with a pharmaceutical carrier, e.g. PBS, as an example of gene therapy (pg 231, col. 1, Animal Model; pg 233, Figure 5).

With respect to the claimed methods, Piechocki et al teach a method of preventing or treating cancer and inducing anti-tumor immunity, reducing tumor growth and prolonging survival period in a mammal, the method comprising administering an effective amount of a pharmaceutical composition comprising an expression vector encoding a truncated human Her-2/neu polypeptide, said polypeptide consisting of the extracellular domain of mature Her-2/neu to laboratory BALB/c mice who received three intramuscular injections of DNA vaccine prior to challenge with Her-2+ D2F2 murine mammary tumor cells over-expressing Her-2/neu (pg 3369, col. 1, Inhibition of Tumor Growth; pg 3371, Figure 3), as measured by CTL response (pg 3372, Figure 5) and production of anti-Her-2/neu-specific antibodies (pg 3370, col. 2). Piechocki et al teach that all tumor-free mice at 10 weeks after tumor challenge were capable of rejecting a second tumor challenge, demonstrating sustained immunity to tumor-associated antigens (pg 3370, col. 2, lines 1-8).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in molecular biology and DNA vaccine immunization methods. Therefore, the level of ordinary skill in this art is high.

Piechocki et al do not teach the use of the entire extracellular domain of mature Her-2/neu (amino acids 1-652). However, at the time of the invention, Chen et al taught the ability of the ordinary artisan to express sub-domains of Her-2/neu, specifically the extracellular domain ($pNeu_E$) or the extracellular and transmembrane domains ($pNeu_{TM}$). Chen et al teach this basic skill in molecular biology applied to rat Her-2/neu; however, the sequence and structure of human Her-2/neu was known at the time and it was/is well within the skill of the ordinary artisan to apply such designed protein subdivision towards human Her-2/neu.

Piechocki et al do not teach the tumor cells to be ovarian cancer. However, nothing non-obvious is seen with substituting breast cancer cells with ovary cancer cells because the art recognizes that both breast and ovary cancer cells overexpress Her-2/neu (Piechocki et al, pg 3367, col. 1, ¶1). Thus, the method of inducing antitumor immunity and prolonging survival period of breast cancer via the use of a Her-2/neu DNA vaccine would also be capable of inducing antitumor immunity and prolonging survival period of ovary cancer, absent evidence to the contrary, as the claims recite the breast and ovary cancers as alternatives (and thus essentially equivalent) and there is nothing in the instant disclosure to clearly distinguish method steps designed specifically for treating breast cancer from method steps designed specifically for treating ovary cancer.

Piechocki et al do not explicitly teach a method of decreasing tumor metastasis as per the use of the human Her-2/neu DNA vaccine. However, absent evidence to the contrary, the capability to decrease tumor metastasis would naturally flow from the DNA vaccine and the method steps performed by Piechocki et al that demonstrated prevention and treatment of cancer, induction of antitumor immunity, reduced tumor growth and prolonged survival periods were also sufficient to decrease tumor metastasis because the DNA vaccine is the same and there is no patentable distinction in the method step by which the vaccine is to administered to the subject so as to clearly exclude the clinically effective method of decreasing tumor metastasis from the

methods of preventing or treating cancer, inducing antitumor immunity, reducing tumor growth and prolonging survival periods.

Piechocki et al do not teach the DNA vaccination method to be performed after a method step of tumor surgery to treat or diagnose a Her-2/neu-over-expressing human cancer. However, at the time of the invention, the art recognized that in the real world clinical setting, human patients will present with tumor disease before being therapeutically treated with a tumor vaccine (Bocchia et al, pg 1174, col. 2, When?, ¶1), and that tumor biopsies are a common clinical practice to diagnose the cancer and/or determine the metastatic spread of the disease, e.g. lymph node biopsy, as a matter of course in determining the mode of treatment. Thus, the claim would have been obvious to one of ordinary skill because a person of ordinary skill has good reason to pursue the known options within his or her technical grasp, e.g. common sense.

The Examiner notes that the pCK vector of Lee et al (2000) is deposited at the KCCM under the Accession No. KCCM-10179 (specification; pg 16, lines 11-12). Thus, the pCK vector of Lee et al (2000) comprising a transmembrane and extracellular domain of human Her-2/neu encoded by SEQ ID NO:2 (Piechocki et al, Erickson et al and Chen et al) would be structurally indistinguishable from pCK_{TM} deposited at the KCCM under the Accession No. KCCM-10396, absent evidence to the contrary. Similarly, the pTV2 vector of Lee et al (1998) comprising a transmembrane and extracellular domain of human Her-2/neu would be structurally indistinguishable from $pTV2_{TM}$ deposited at the KCCM under the Accession No. KCCM-10393, absent evidence to the contrary.

The Examiner notes that the substitution of E1t or E2t for a transmembrane and extracellular domain of human Her-2/neu encoded by SEQ ID NO:2 (Piechocki et al, Erickson et al and Chen et al) into the pTV2 bi-cistronic expression plasmid comprising a GM-CSF gene (Lee et al, 1998) would be structurally indistinguishable from $pCK_{TM\text{-}GMCSF}$ recited in claim 37.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute the expression vector of Piechocki et al with the pTV2 or pCK expression vectors as taught by Lee et al (1998

and 2000) with a reasonable chance of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Lee et al (1998 and 2000) teach the ability of such vectors for use as *in vivo* DNA delivery vehicles, e.g. DNA vaccines. Furthermore, nothing non-obvious is seen with replacing one expression vector for another expression vector because the Her-2/neu gene is under the same regulatory control, specifically the CMV promoter, in the pTV2 vector as is also present in the pCK vector, and thus the substitution of a pCK vector for a pTV2 vector would yield predictable results as the vectors are functionally equivalent. An artisan would be motivated to use the expression vectors of Lee et al (1998 and 2000) because Lee et al teach that, for example, the newly developed pCK vector efficiently expressed the exogenously added gene *in vivo*, and reproducibly produced much higher levels of the target polypeptide than all expression vectors tested so far, including commercially available HCMV IE promoter-based plasmids and those using housekeeping gene promoters. Furthermore, Lee et al suggest that pCK provides clear advantages over other previously developed plasmids, and would not only significantly increase therapeutic effects at a given dose, but also lower the costs of production, and thus treatment. With respect to the broad applicability for *in vivo* gene therapy, Lee et al anticipate the vector should be useful for gene therapy for any disease that can be treated with a reasonable level of gene expression in a transient manner in a localized area (pg 234, Discussion). Similarly, Lee et al (1998) teach that co-delivery of GM-CSF gene using the pTV2 expression vector elicited higher lymphoproliferative responses to a gene of interest than without GM-CSF. Co-delivery of the GM-CSF gene enhances T-helper cell responses in DNA-based immunization (pg 8434, col.s 1-2).

It also would have been obvious to one of ordinary skill in the art to try substituting the Her-2/neu extracellular domain of Piechocki et al for the entire extracellular domain of Her-2/neu because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention and "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipate success, it is likely that product not of innovation but of ordinary skill and common sense." An artisan would be motivated to try substituting the Her-2/neu extracellular domain of Piechocki et al for the entire extracellular domain of Her-2/neu because

the extracellular domain of Piechocki et al is missing ca.147 amino acids which would likely provide additional antigenic peptide motifs and/or improve the immunization response to the DNA vaccine.

It also would have been obvious to one of ordinary skill in the art to try using a pTV2 or pCK expression vector encoding a truncated human Her-2/neu polypeptide, said polypeptide consisting of an extracellular domain or the transmembrane and extracellular domains of the mature human Her-2/neu extracellular domain in methods of preventing or treating cancer, inducing anti-tumor immunity, reducing tumor growth, decreasing tumor metastasis and prolonging survival in a human subject suffering from a Her-2/neu-over-expressing human cancer because "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipate success, it is likely that product not of innovation but of ordinary skill and common sense." An artisan would be motivated to try using a pTV2 or pCK expression vector encoding a truncated human Her-2/neu polypeptide, said polypeptide consisting of of an extracellular domain or the transmembrane and extracellular domains of the mature human Her-2/neu extracellular domain in methods of preventing or treating cancer, inducing anti-tumor immunity, reducing tumor growth, decreasing tumor metastasis and prolonging survival in a human subject suffering from a Her-2/neu-over-expressing human cancer because ErbB-2 has long been recognized as a target of immunotherapy in that several human cancers, including breast, ovarian, and lung cancers overexpress ErbB-2, which is associated with aggressive disease and poor prognosis (Piechocki et al, pg 3367, col. 1, Introduction).

Thus, the invention as a whole is *prima facie* obvious.

Conclusion

8. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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